Product Information

HARVONI® (ledipasvir and sofosbuvir) tablets

NAME OF THE MEDICINE

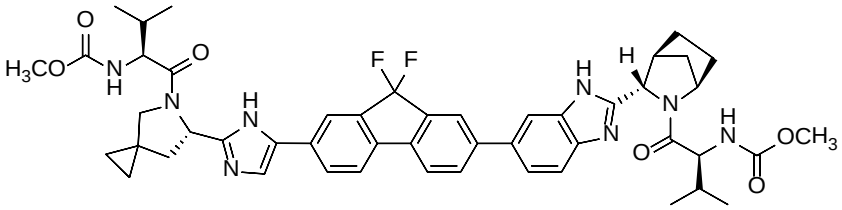
HARVONI (ledipasvir/sofosbuvir 90 mg/400 mg) tablets.

The active substances in HARVONI tablets are ledipasvir and sofosbuvir.

Ledipasvir is an HCV NS5A inhibitor and sofosbuvir is a nucleotide inhibitor of HCV NS5B RNA-dependent RNA polymerase.

The chemical name of ledipasvir is Methyl [(2*S*)-1-{(6*S*)-6-[5-(9,9-difluoro-7- {2-[(1*R*,3*S*,4*S*)-2-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-azabicyclo[2.2.1]hept-3-yl]-1*H*-benzimidazol-6-yl}-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-5-azaspiro[2.4]hept-5-yl}-3-methyl-1-oxobutan-2-yl]carbamate.

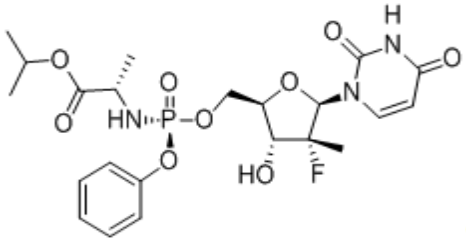
It has a molecular formula of $C_{49}H_{54}F_2N_8O_6$ and a molecular weight of 889.00. It has the following structural formula**:**



CAS registry number: 1256388-51-8

Ledipasvir is practically insoluble (<0.1 mg/mL) across the pH range of 3.0-7.5 and is slightly soluble below pH 2.3 (1.1 mg/mL). The partition coefficient (log P) for ledipasvir is 3.8 and the pKa1 is 4.0 and pKa2 is 5.0.

The chemical name of sofosbuvir is (*S*)-Isopropyl 2-((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate. It has a molecular formula of $C_{22}H_{29}FN_3O_9P$ and a molecular weight of 529.45. It has the following structural formula:



CAS registry number: 1190307-88-0

Sofosbuvir is a white to off-white powder with a solubility of ≥ 2 mg/mL across the pH range of 2-7.7 at 37 °C. The partition coefficient (log P) for sofosbuvir is 1.62 and the pKa is 9.3.

DESCRIPTION

HARVONI tablets contain the following ingredients as excipients:

Tablet core: silicon dioxide, copovidone, croscarmellose sodium, lactose, magnesium stearate and microcrystalline cellulose.

Film-coating: polyvinyl alcohol, macrogol 3350, titanium dioxide, purified talc, and sunset yellow FCF aluminium lake.

Each HARVONI tablet is film-coated and orange in colour. The tablets are diamond shaped debossed with "GSI" on one side and the number "7985" on the other side. The tablets are supplied in bottles with child resistant closures.

PHARMACOLOGY

Pharmacotherapeutic group: Antivirals for systemic use; direct acting antivirals, other antivirals, ATC code:J05AX65.

Mechanism of action

Ledipasvir is a HCV inhibitor targeting the HCV NS5A protein, which is essential for both RNA replication and the assembly of HCV virions. Biochemical confirmation of NS5A inhibition of ledipasvir is not currently possible as NS5A has no enzymatic function. *In vitro* resistance selection and cross-resistance studies indicate ledipasvir targets NS5A as its mode of action.

Sofosbuvir is a pangenotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated by HCV NS5B and acts as a chain terminator. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a and 4a with an IC_{50} value ranging from 0.7 to 2.6 μM. GS-461203 is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Antiviral activity *in vitro*

The EC_{50} values of ledipasvir and sofosbuvir against full-length or chimeric replicons encoding NS5A and NS5B sequences from clinical isolates are detailed in Table 1. The presence of 40% human serum reduced anti-HCV activity of ledipasvir by 12-fold against genotype 1a HCV replicon.

Table 1 Activity of ledipasvir and sofosbuvir against chimeric replicons

Genotype replicons	Ledipasvir activity (EC_{50}, nM)		Sofosbuvir activity (EC_{50}, nM)	
	Stable replicons	NS5A transient replicons Median (range)[a]	Stable replicons	NS5B transient replicons Median (range)[a]
Genotype 1a	0.031	0.018 (0.009-0.085)	40	62 (29-128)
Genotype 1b	0.004	0.006 (0.004-0.007)	110	102 (45-170)
Genotype 2a	21-249	-	50	29 (14-81)

Genotype replicons	Ledipasvir activity (EC_{50}, nM)		Sofosbuvir activity (EC_{50}, nM)	
	Stable replicons	NS5A transient replicons Median (range)[a]	Stable replicons	NS5B transient replicons Median (range)[a]
Genotype 2b	16-530[b]	-	15[b]	-
Genotype 3a	168	-	50	81 (24-181)
Genotype 4a	0.39	-	40	-
Genotype 4d	0.60	-	-	-
Genotype 5a	0.15[b]	-	15[b]	-
Genotype 6a	1.1[b]	-	14[b]	-
Genotype 6e	264[b]	-	-	-

a. Transient replicons carrying NS5A or NS5B from patient isolates.

b. The chimeric replicons carrying NS5A genes from genotype 2b, 5a, 6a and 6e were used for testing ledipasvir while the chimeric replicons carrying NS5B genes from genotype 2b, 5a or 6a were used for testing sofosbuvir.

Drug Resistance

In Cell Culture:

HCV replicons with reduced susceptibility to ledipasvir have been selected in cell culture for genotype 1a and 1b. Reduced susceptibility to ledipasvir was associated with the primary NS5A substitution Y93H in both genotype 1a and 1b. Additionally a Q30E substitution emerged in genotype 1a replicons. Site-directed mutagenesis of the Y93H in both genotype 1a and 1b as well as the Q30E substitution in genotype 1a conferred high levels of reduced susceptibility to ledipasvir (fold change in EC_{50} greater than 500-fold).

HCV replicons with reduced susceptibility to sofosbuvir have been selected in cell culture for multiple genotypes including 1b, 2a, 2b, 3a, 4a, 5a and 6a. Reduced susceptibility to sofosbuvir was associated with the primary NS5B substitution S282T in all replicon genotypes examined. Site-directed mutagenesis of the S282T substitution in replicons of 8 genotypes including 1a, 1b, 2a, 2b, 3a, 4a, 5a and 6a conferred 2- to 18-fold reduced susceptibility to sofosbuvir and reduced the replication capacity by 89% to 99% compared to the corresponding wild-type. In biochemical assays, recombinant NS5B polymerase from genotypes 1b, 2a, 3a and 4a expressing the S282T substitution showed reduced susceptibility to GS-461203 compared to respective wild-types.

In Clinical Studies:

<u>Genotype 1</u>

In a pooled analysis of patients who received HARVONI in Phase 3 trials (ION-3, ION-1 and ION-2), 37 patients (29 with genotype 1a and 8 with genotype 1b) qualified for resistance analysis due to virologic failure or early study drug discontinuation and having HCV RNA > 1000 IU/ml. Post-baseline NS5A and NS5B deep sequencing data (assay cutoff of 1%) were available for 37/37 and 36/37 patients, respectively.

NS5A resistance-associated variants (RAVs) were observed in post-baseline isolates from 29/37 patients not achieving SVR. Of the 29 genotype 1a patients who qualified for resistance testing,

22/29 (76%) patients harbored one or more NS5A RAVs at positions K24, Q30, L31, S38 and Y93 at failure, while the remaining 7/29 patients had no NS5A RAVs detected at failure. The most common variants were Q30R, Y93H, L31M, Y93N and Q30H. Of the 8 genotype 1b patients who qualified for resistance testing, 7/8 (88%) harbored one or more NS5A RAVs at positions L31 and Y93 at failure, while 1/8 patients had no NS5A RAVs at failure. The most common variant was Y93H. Among the 8 patients who had no NS5A RAVs at failure, 7 patients received 8 weeks of treatment (N=3 with HARVONI; N=4 with HARVONI +ribavirin) and 1 patient received HARVONI for 12 weeks. In phenotypic analyses, post-baseline isolates from patients who harbored NS5A RAVs at failure showed 20- to >243-fold reduced susceptibility to ledipasvir.

Among post-transplant patients with compensated liver disease or patients with decompensated liver disease (pre- and post-transplant) (SOLAR-1 and SOLAR-2 trials), relapse was associated with the detection of one or more of the following NS5A RAVs: K24R, M28T, Q30R/H/K, L31V, H58D and Y93H/C in 12/14 genotype 1a patients, and L31M, Y93H/N in 6/6 genotype 1b patients.

The NS5B nucleoside inhibitor resistance associated variants (NS5B NI RAVs) L159F and V321A were each detected in one patient with genotype 1a infection in the Phase 3 trials (ION-1, ION-2, and ION-3). The single L159F and V321A variants demonstrated 1.2- and 1.2-fold change in EC_{50} to sofosbuvir in genotype 1a replicon, respectively. The NS5B substitution E237G was detected in 3 patients (1 genotype 1b and 2 genotype 1a) in the Phase 3 trials (ION-3, ION-1 and ION-2) and 3 patients (all genotype 1a) in the phase 2 trials of patients with advanced liver disease (SOLAR-1 and SOLAR-2) at the time of relapse. The E237G substitution showed a 1.3-fold reduction in susceptibility to sofosbuvir in the genotype 1a replicon assay. The clinical significance of these substitutions is currently unknown.

The NS5B NI RAV S282T in NS5B was not detected in any failure isolate from theION-1, ION-2, ION-3, SOLAR-1 or SOLAR-2 trials. However, the NS5B S282T substitution in combination with NS5A RAVs L31M, Y93H and Q30L were detected in one patient at failure following 8 week treatment with HARVONI from the Phase 2 trial LONESTAR. This patient was subsequently retreated with HARVONI + ribavirin for 24 weeks and achieved SVR following retreatment.

Genotype 2, 3, 4, 5, and 6

Resistance analysis was performed for virologic failures in clinical trials with genotype 2, 3, 4, 5 and 6 CHC. Patients in these trials were treated with HARVONI or HARVONI+RBV for 12 weeks (see CLINICAL TRIALS).

Genotype 2: None of the genotype 2 patients experienced virologic failure in the LEPTON study.Genotype 3: Of the 17 patients who experienced virologic failures in the ELECTRON-2 study, one patient developed the NS5A RAV Y93C (1.1%), one patient developed the NS5B NI RAV S282T and one patient developed the NS5B NI RAV L159F.

Genotype 4: Of the 3 patients who experienced virologic failure in Study 1119, one patient developed the NS5B NI RAV S282T along with the NS5A RAV Y93C. In SOLAR-2 trial, one patient with genotype 4d developed NS5B substitution E237G at the time of relapse. The clinical significance of this substitution is currently unknown.

Genotype 5: NS5A sequencing was successful in 1 of 2 virologic failure patients in Study 1119. This patient developed NS5B NI RAVs S282T (1.6%) and M289I (16%).

Genotype 6: Virologic failure occurred in one patient in the ELECTRON-2 study who discontinued treatment early at approximately Week 8 and subsequently relapsed in Study ELECTRON-2. This patient developed NS5B NI RAV S282T.

Effect of Baseline HCV Polymorphisms on Treatment Outcome

Genotype 1

Analyses were conducted to explore the association between pre-existing baseline NS5A resistance-associated variants (RAVs) and treatment outcome. In the pooled analysis of the Phase 3 trials (ION-1, ION-2 and ION-3), 256/1618 (16%) patients had baseline NS5A RAVs identified by population or deep sequencing irrespective of subtype.

In treatment-naïve patients in ION-3 with NS5A RAVs, SVR12 rates of 89% (34/38) after 8 weeks and 96% (66/69) after 12 weeks of therapy were observed with HARVONI. No association between any individual NS5A RAV and treatment outcome was observed.

In treatment-experienced patients in ION-2 who had baseline NS5A RAVs, an SVR12 rate of 76% (13/17) after 12 weeks of therapy was observed with HARVONI. When NS5A RAVs were grouped by their EC_{50} fold change from wild-type, among those treatment-experienced patients with any NS5A RAV conferring <100-fold resistance *in vitro*, 4/4 (100%) patients achieved SVR following 12 weeks of treatment with HARVONI. Among those treatment experienced patients with any NS5A RAV conferring ≥100-fold resistance, 9/13 (69%) patients achieved SVR following 12 weeks of treatment with HARVONI compared to 93/96 (97%) in those without any baseline RAVs or RAVs conferring a fold-change of ≤ 100. In another study in treatment-experienced patients with compensated cirrhosis (SIRIUS, N=77), 8/8 (100%) patients with baseline NS5A RAVs conferring >100-fold reduced susceptibility to ledipasvir achieved SVR following 12 weeks of treatment with HARVONI+RBV.

Among post-transplant patients with compensated liver disease (SOLAR-1 and SOLAR-2 studies), no relapse occurred in patients with baseline NS5A RAVs (N=23) following 12 weeks of treatment with HARVONI+RBV. Among patients with decompensated liver disease (pre- and post-transplant), 4/16 (25%) patients with NS5A RAVs conferring >100-fold resistance relapsed after 12 weeks treatment with HARVONI+RBV compared to 7/120 (6%) in those without any baseline NS5A RAVs or RAVs conferring a fold-change of ≤100.

The group of NS5A RAVs that conferred >100-fold shift were defined as any of the following substitutions in genotype 1a (M28A/G, Q30E/G/H/K/R, L31I/M/V, P32L, H58D, Y93C/H/N/S) or in genotype 1b (P58D, A92K, Y93H).

The NS5B NI RAV S282T was not detected in the baseline NS5B sequence of any patient in Phase 3 trials (ION-1, ION-2, ION-3) by population or deep sequencing. SVR was achieved in all 24 patients (N=21 with L159F and N=3 with N142T) who had baseline NS5B NI RAVs.

Genotype 2, 3, 4, 5 and 6

Baseline NS5A RAVs did not have a clinically meaningful effect on treatment outcome in clinical studies of patients with genotype 2, 4, 5 or 6 CHC. For patients with genotype 3 CHC, the role of baseline NS5A RAVs varied depending on the patient population.

For patients with genotype 2, 4, 5 and 6 CHC, SVR was achieved in 14/14 (100%), 25/28 (89%), 7/8 (88%) and 17/18 (94%) patients who had baseline NS5A RAVs following 12 weeks treatment with HARVONI, respectively. The specific baseline NS5A RAVs observed in patients

with virologic failure were L28M/V and L30R for genotype 4, L31M for genotype 5 and F28V for genotype 6.

Among treatment-naïve patients with genotype 3 CHC who were treated with HARVONI+RBV for 12 weeks, SVR was achieved in 4/4 (100%) patients with baseline NS5A RAVs. Among treatment-experienced patients with genotype 3 CHC, SVR was achieved in 4/6 (67%) and 37/44 (84%) patients with or without baseline NS5A RAVs, respectively. The specific baseline NS5A RAVs observed in patients with virologic failure were S24G, A30K, L31M and Y93H.

The NS5B NI RAV S282T was not detected in the baseline NS5B sequence of any patient with genotype 2, 3, 4, 5 or 6 CHC in clinical trials by population or deep sequencing. For patients with genotype 2, 3 and 5 CHC, SVR was achieved in all 14 patients who had baseline NS5B NI RAVs (N=4 with M289I in genotype 2; N=1 with N142T in genotype 3; N=7 with N142T and N=2 with M289I in genotype 5).

Relapse occurred in 2/3 genotype 4 patients who had the baseline NS5B NI RAV V321I along with two baseline NS5A RAVs.

In patients with genotype 6 CHC, SVR was achieved in one patient each with the baseline NS5B NI RAVs M289L+S282G or M289L+V321A and 13/14 patients with M289L/I.

Cross-resistance:

Ledipasvir was fully active against the sofosbuvir-associated resistance substitution S282T in NS5B while all ledipasvir resistance-associated substitutions in NS5A were fully susceptible to sofosbuvir. Both sofosbuvir and ledipasvir were fully active against substitutions associated with resistance to other classes of direct acting antivirals with different mechanisms of action, such as NS5B non-nucleoside inhibitors and NS3 protease inhibitors. NS5A substitutions conferring resistance to ledipasvir may reduce the antiviral activity of other NS5A inhibitors. The efficacy of HARVONI has not been established in patients who have previously failed treatment with other regimens that include an NS5A inhibitor.

Pharmacokinetics

Absorption

The pharmacokinetic properties of ledipasvir, sofosbuvir and the predominant circulating metabolite GS-331007 have been evaluated in healthy adult patients and in patients with chronic hepatitis C. Following oral administration of HARVONI, ledipasvir median peak concentrations were observed 4.0 to 4.5 hours post-dose. Sofosbuvir was absorbed quickly and the peak median plasma concentration was observed ~ 0.8 to 1 hour post-dose. Median peak plasma concentration of GS-331007 was observed between 3.5 to 4 hours post-dose.

Based on the population pharmacokinetic analysis in HCV-infected patients, geometric mean steady-state AUC_{0-24} for ledipasvir (N=2113), sofosbuvir (N=1542), and GS-331007 (N=2113) were 7290, 1320 and 12,000 ng•hr/ml, respectively. Steady-state C_{max} for ledipasvir, sofosbuvir and GS-331007 were 323, 618 and 707 ng/ml, respectively. Sofosbuvir and GS-331007 AUC_{0-24} and C_{max} were similar in healthy adult patients and patients with HCV infection. Relative to healthy subjects (N=191), ledipasvir AUC_{0-24} and C_{max} were 24% lower and 32% lower, respectively in HCV-infected patients.

Ledipasvir AUC is dose proportional over the dose range of 3 to 100 mg. Sofosbuvir and GS-331007 AUCs are near dose proportional over the dose range of 200 mg to 1,200 mg.

Distribution

Ledipasvir is >99.8% bound to human plasma proteins. After a single 90 mg dose of [^{14}C]-ledipasvir in healthy subjects, the blood to plasma ratio of ^{14}C-radioactivity ranged between 0.51 and 0.66.

Sofosbuvir is approximately 61-65% bound to human plasma proteins and the binding is independent of drug concentration over the range of 1 µg/mL to 20 µg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [^{14}C]-sofosbuvir in healthy subjects, the blood to plasma ratio of ^{14}C-radioactivity was approximately 0.7.

Metabolism

In vitro, no detectable metabolism of ledipasvir was observed by human CYP1A2, CYP2C8, CYP2C9, CYP 2C19, CYP2D6 and CYP3A4. Evidence of slow oxidative metabolism via an unknown mechanism has been observed. Following a single dose of 90 mg [^{14}C]-LDV, systemic exposure was almost exclusively to the parent drug (>98%). Unchanged ledipasvir is the major species present in faeces.

Sofosbuvir is extensively metabolised in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. The metabolic activation pathway involves sequential hydrolysis of the carboxyl ester moiety catalysed by human cathepsin A (CatA) or carboxylesterase 1 (CES1) and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 (HINT1) followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity in vitro. After a single 400 mg oral dose of [^{14}C]-sofosbuvir, GS-331007 accounted for approximately >90% of total systemic exposure.

Excretion

Following a single 90 mg oral dose of [^{14}C]-ledipasvir, mean total recovery of the [^{14}C]-radioactivity in faeces and urine was approximately 87%, with most of the radioactive dose recovered from faeces (approximately 86%). Unchanged ledipasvir excreted in faeces accounted for a mean of 70% of the administered dose and the oxidative metabolite M19 accounted for 2.2% of the dose. These data suggest that biliary excretion of unchanged ledipasvir is a major route of elimination with renal excretion being a minor pathway (approximately 1%). The median terminal half-life of ledipasvir was 47 hours.

Following a single 400 mg oral dose of [^{14}C]-sofosbuvir, mean total recovery of the dose greater than 92%, consisting of approximately 80%, 14%, and 2.5% recovered in urine, faeces and expired air, respectively. The majority of the sofosbuvir dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as sofosbuvir. This data indicate that renal clearance is the major elimination pathway for GS-331007. The median terminal half-lives of sofosbuvir and GS-331007 were 0.4 and 27 hours, respectively.

Effect of food

Relative to fasting conditions, the administration of a single dose of HARVONI with a moderate fat (~600 kcal, 25% to 30% fat) or high fat (~1000 kcal, 50% fat) meal did not substantially affect

the sofosbuvir C_{max} and $AUC_{0\text{-}inf}$. The exposures of GS-331007 and ledipasvir were not altered in the presence of either meal type. The response rates in Phase 3 trials were similar in HCV-infected patients who received HARVONI with food or without food. HARVONI can be administered without regard to food.

Age, Gender and Ethnicity

No clinically relevant pharmacokinetic differences due to race have been identified for ledipasvir, sofosbuvir or GS-331007. No clinically relevant pharmacokinetic differences due to gender have been identified for sofosbuvir or GS-331007.

AUC and C_{max} of ledipasvir were 77% and 58% higher respectively in females than males; however, the relationship between gender and ledipasvir exposures was not considered clinically relevant as high response rates (SVR >90%) were achieved in males across the Phase 3 studies.

Elderly Patients

Population pharmacokinetic analysis in HCV-infected patients showed that within the age range (18 to 80 years) analysed, age did not have a clinically relevant effect on the exposure to ledipasvir, sofosbuvir or GS-331007. Clinical studies of HARVONI included 351 patients aged 65 and over. The response rates observed for patients ≥65 years of age were similar to that of subjects <65 years of age, across treatment groups.

Paediatric Patients

The pharmacokinetics of ledipasvir, sofosbuvir and GS-331007 in paediatric patients have not been established.

Patients with Impaired Renal Function

The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in HCV negative patients with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault). No clinically relevant differences in ledipasvir pharmacokinetics were observed between healthy patients and patients with severe renal impairment. No dose adjustment of ledipasvir is required for patients with mild, moderate or severe renal impairment. The pharmacokinetics of sofosbuvir were studied in HCV negative patients with mild (eGFR ≥ 50 and < 80 mL/min/1.73m^2), moderate (eGFR ≥ 30 and < 50 mL/min/1.73m^2), severe renal impairment (eGFR < 30 mL/min/1.73m^2) and patients with end stage renal disease (ESRD) requiring haemodialysis following a single 400 mg dose of sofosbuvir. Relative to patients with normal renal function (eGFR > 80 mL/min/1.73m^2), the sofosbuvir $AUC_{0\text{-}inf}$ was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 $AUC_{0\text{-}inf}$ was 55%, 88% and 451% higher, respectively. In patients with ESRD, relative to patients with normal renal function, sofosbuvir and GS-331007 $AUC_{0\text{-}inf}$ was 28% and 1280% higher when sofosbuvir was dosed 1 hour before haemodialysis compared with 60% and 2070% higher when sofosbuvir was dosed 1 hour after haemodialysis. Haemodialysis is required for the elimination of GS-331007 in patients with ESRD, with a 4 hour haemodialysis removing approximately 18% of administered dose. No dose recommendations can be given for patients with severe renal impairment eGFR<30mL/min/1.73m^2 or with end stage renal disease requiring haemodialysis due to higher exposure of the predominant sofosbuvir metabolite.

Patients with Hepatic Impairment

The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in HCV negative patients with severe hepatic impairment (Child Pugh Class C). Ledipasvir plasma exposure ($AUC_{0\text{-}inf}$) was similar in patients with severe hepatic impairment and control patients with normal hepatic function. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of ledipasvir. No dose adjustment of ledipasvir is recommended for patients with mild, moderate or severe hepatic impairment.

The pharmacokinetics of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected patients with moderate and severe hepatic impairment (Child Pugh Class B and C). Relative to patients with normal hepatic function, the sofosbuvir $AUC_{0\text{-}24}$ was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 $AUC_{0\text{-}24}$ was 18% and 9% higher, respectively. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of sofosbuvir and GS-331007. No dose adjustment of sofosbuvir is recommended for patients with mild, moderate or severe hepatic impairment.

Assessment of Drug Interactions

The effects of coadministered drugs on the exposure of ledipasvir, sofosbuvir and GS-331007 are shown in Table 2. The effects of ledipasvir or sofosbuvir on the exposure of coadministered drugs are shown in Table 3.

Table 2 Drug Interactions: Changes in Pharmacokinetic Parameters for Ledipasvir, Sofosbuvir and the Predominant Circulating Metabolite GS-331007 in the Presence of the Coadministered Drug[a]

Co-administered Drug	Dose of Coadministered Drug (mg)	LDV Dose (mg)	SOF Dose (mg)	N	Mean Ratio (90% CI) of Ledipasvir, Sofosbuvir and GS-331007 PK With/Without Coadministered Drug No Effect=1.00			
						Cmax	AUC	Cmin
Abacavir/lamivudine	600/300 once daily	90 once daily	400 once daily	13	ledipasvir	1.10 (1.01, 1.19)	1.18 (1.10, 1.28)	1.26 (1.17, 1.36)
					sofosbuvir	1.08 (0.85, 1.35))	1.21 (1.01, 1.35)	NA
					GS-331007	1.00 (0.94, 1.07)	1.05 (1.01, 1.09)	1.08 (1.01, 1.14)
Atazanavir/ritonavir	300/100 once daily	90 once daily	400 once daily	30	ledipasvir	1.98 (1.78, 2.20)	2.13 (1.89, 2.40)	2.36 (2.08, 2.67)
					sofosbuvir	0.96 (0.88, 1.05)	1.08 (1.02, 1.15)	NA

Co-administered Drug	Dose of Coadministered Drug (mg)	LDV Dose (mg)	SOF Dose (mg)	N	Mean Ratio (90% CI) of Ledipasvir, Sofosbuvir and GS-331007 PK With/Without Coadministered Drug No Effect=1.00			
						Cmax	AUC	Cmin
					GS-331007	1.13(1.08, 1.19)	1.23 (1.18, 1.29)	1.28 (1.21, 1.36)
Atazanavir/ ritonavir + tenofovir disoproxil fumarate/ emtricitabine[b]	300/100 + 300/200 once daily	90 once daily	400 once daily	24	ledipasvir	1.68 (1.54, 1.84)	1.96 (1.74, 2.21)	2.18 (1.91, 2.50)
					sofosbuvir	1.01 (0.88, 1.15)	1.11 (1.02, 1.21)	NA
					GS-331007	1.17 (1.12, 1.23)	1.31 (1.25, 1.36)	1.42 (1.34, 1.49)
Cyclosporin	600 single dose	ND	400 single dose	19	sofosbuvir	2.54 (1.87, 3.45)	4.53 (3.26, 6.30)	N/A
					GS-331007	0.60 (0.53, 0.69)	1.04 (0.90, 1.20)	NA
Darunavir/ ritonavir	800/100 once daily	90 once daily	ND	23	ledipasvir	1.45 (1.34, 1.56)	1.39 (1.28. 1.49)	1.39(1.29, 1.51)
		ND	400 once daily	18	sofosbuvir	1.45 (1.10. 1.92)	1.34 (1.12, 1.59)	NA
					GS-331007	0.97 (0.90, 1.05)	1.24 (1.18, 1.30)	NA
Darunavir/ ritonavir + tenofovir disoproxil fumarate/ emtricitabine[b]	800/100 + 300/200 once daily	90 once daily	400 once daily	23	ledipasvir	1.11 (0.99, 1.24)	1.12 (1.00, 1.25)	1.17 (1.04, 1.31)
					sofosbuvir	0.63 (0.52, 0.75)	0.73 (0.65, 0.82)	NA
					GS-331007	1.10 (1.04, 1.16)	1.20 (1.16, 1.24)	1.26 (1.20, 1.32)
Dolutegravir +tenofovir disproxil	50 + 300/200 once daily	90 once daily	400 once daily	29	ledipasvir	0.85 (0.81, 0.90)	0.89 (0.84, 0.95)	0.89 (0.84, 0.95)

Co-administered Drug	Dose of Coadministered Drug (mg)	LDV Dose (mg)	SOF Dose (mg)	N	Mean Ratio (90% CI) of Ledipasvir, Sofosbuvir and GS-331007 PK With/Without Coadministered Drug No Effect=1.00			
						Cmax	AUC	Cmin
fumarate/ emtricitabine					sofosbuvir	1.06 (0.92, 1.21)	1.09 (1.00, 1.19)	NA
					GS-331007	0.99 (0.95, 1.03)	1.06 (1.03, 1.09)	1.06 (1.03, 1.10)
Tenofovir disoproxil fumarate/ emtricitabine/ efavirenz[c]	300/200/600 once daily	90 once daily	400 single dose	14	ledipasvir	0.66 (0.59, 0.75)	0.66 (0.59, 0.75)	0.66 (0.57, 0.76)
					sofosbuvir	1.03 (0.87, 1.23)	0.94 (0.81, 1.10)	NA
					GS-331007	0.86 (0.76, 0.96)	0.90 (0.83. 0.97)	1.07 (1.02, 1.13)
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide	150/150/200/10 once daily	90 once daily	400 once daily	30	ledipasvir	1.65 (1.53, 1.78)	1.79 (1.64, 1.96)	1.93 (1.74, 2.15)
					sofosbuvir	1.28 (1.13, 1.47)	1.47 (1.35,1.59)	NA
					GS-331007	1.29 (1.24, 1.35)	1.48 (1.44, 1.53)	1.66 (1.60, 1.73)
Tenofovir disoproxil fumarate/ emtricitabine/ rilpivirine[d]	300/200/ 25 once daily	90 once daily	400 once daily	15	ledipasvir	1.01 (0.95, 1.07)	1.08 (1.02, 1.15)	1.16 (1.08, 1.25)
					sofosbuvir	1.05 (0.93, 1.20)	1.10 (1.01, 1.21)	NA
					GS-331007	1.06 (1.01, 1.11)	1.15 (1.11, 1.19)	1.18 (1.13, 1.24)
Famotidine	40 single dose simultaneously with HARVONI	90 single dose	400 single dose	12	ledipasvir	0.80 (0.69, 0.93)	0.89 (0.76, 1.06)	NA
					sofosbuvir	1.15 (0.88, 1.50)	1.11 (1.00, 1.24)	NA

Co-administered Drug	Dose of Coadministered Drug (mg)	LDV Dose (mg)	SOF Dose (mg)	N	Mean Ratio (90% CI) of Ledipasvir, Sofosbuvir and GS-331007 PK With/Without Coadministered Drug No Effect=1.00			
						Cmax	AUC	Cmin
					GS-331007	1.06 (0.97, 1.14)	1.06 (1.02, 1.11)	NA
	40 single dose 12 hours prior to HARVONI			12	ledipasvir	0.83 (0.69, 1.00)	0.98 (0.80, 1.20)	NA
					sofosbuvir	1.00 (0.76, 1.32)	0.95 (0.82, 1.10)	NA
					GS-331007	1.13 (1.07, 1.20)	1.06 (1.01, 1.12)	NA
Methadone	30 to 130 daily	ND	400 once daily	14	sofosbuvir	0.95 (0.68, 1.33)	1.30 (1.00, 1.69)	NA
					GS-331007	0.73 (0.65, 0.83)	1.04 (0.89, 1.22)	NA
Omeprazole	20 once daily simultaneously with HARVONI	90 single dose	400 single dose	16	ledipasvir	0.89 (0.61, 1.30)	0.96 (0.66, 1.39)	NA
					sofosbuvir	1.12 (0.88, 1.42)	1.00 (0.80, 1.25)	NA
					GS-331007	1.14 (1.01, 1.29)	1.03 (0.96, 1.12)	NA
Raltegravir	400 twice daily	90 once daily	ND	28	ledipasvir	0.92 (0.85, 1.00)	0.91 (0.84, 1.00)	0.89 (0.81, 0.98)
		ND	400 single dose	19	sofosbuvir	0.87 (0.71, 1.08)	0.95 (0.82, 1.09)	NA
					GS-331007	1.09 (0.99, 1.19)	1.02 (0.97, 1.08)	NA
Rifampicin[e]	600 once daily	90 single dose	ND	31	ledipasvir	0.65 (0.56, 0.76)	0.41 (0.36, 0.48)	NA

Co-administered Drug	Dose of Coadministered Drug (mg)	LDV Dose (mg)	SOF Dose (mg)	N	Mean Ratio (90% CI) of Ledipasvir, Sofosbuvir and GS-331007 PK With/Without Coadministered Drug No Effect=1.00			
						Cmax	AUC	Cmin
Simeprevir	150 once daily	30 once daily	ND	22	ledipasvir	1.81 (1.69, 2.94)	1.92 (1.77, 2.07)	NA
Tacrolimus	5 single dose	ND	400 single dose	16	sofosbuvir	0.97 (0.65, 1.43)	1.13 (0.81, 1.57)	NA
					GS-331007	0.97 (0.83, 1.14)	1.00 (0.87, 1.13)	NA

NA = not available/not applicable, ND = not dosed.
a. All interaction studies conducted in healthy volunteers
b. Data generated from simultaneous dosing with HARVONI. Staggered administration (12 hours apart) of atazanavir/ritonavir + tenofovir disoproxil fumarate/ emtricitabine/ or darunavir/ritonavir + tenofovir disoproxil fumarate/emtricitabine and HARVONI provided similar results.
c. Administered as ATRIPLA.
d. Administered as EVIPLERA.
e. This study was conducted in the presence of two other investigational HCV direct-acting agents.

Table 3 Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Ledipasvir, Sofosbuvir or HARVONI[a]

Co-administered Drug	Dose of Coadministered Drug (mg)	LDV Dose (mg)	SOF Dose (mg)	N	Mean Ratio (90% CI) of Coadministered drug PK With/Without Ledipasvir, Sofosbuvir or HARVONI No Effect=1.00		
					C_{max}	AUC	C_{min}
Abacavir/lamivudine	Abacavir 600 once daily	90 once daily	400 once daily	15	0.92 (0.87, 0.97)	0.90 (0.85, 0.94)	NA
	Lamivudine 300 once daily				0.93 (0.87, 1.00)	0.94 (0.90, 0.98)	1.12 (1.05, 1.20)
Atazanavir/ ritonavir	300/100 once daily	90 once daily	400 once daily	30	1.07 (1.00, 1.15)	1.33 (1.25, 1.42)	1.75 (1.58, 1.93)
Atazanavir/ ritonavir + tenofovir disoproxil fumarate/ emtricitabine[b,c]	atazanavir 300 once daily	90 once daily	400 once daily	24	1.07 (0.99, 1.14)	1.27 (1.18, 1.37)	1.63 (1.45, 1.84)
	ritonavir 100 once daily				0.86 (0.79, 0.93)	0.97 (0.89, 1.05)	1.45 (1.27, 1.64)

Co-administered Drug	Dose of Coadministered Drug (mg)	LDV Dose (mg)	SOF Dose (mg)	N	Mean Ratio (90% CI) of Coadministered drug PK With/Without Ledipasvir, Sofosbuvir or HARVONI No Effect=1.00		
					C_{max}	AUC	C_{min}
	emtricitabine 200 once daily				0.98 (0.94, 1.02)	1.00 (0.97, 1.04)	1.04 (0.96, 1.12)
	tenofovir disoproxil fumarate 300 once daily				1.47 (1.37, 1.58)	1.35 (1.29, 1.42)	1.47 (1.38, 1.57)
Cyclosporin	600 single dose	ND	400 single dose	19	1.06 (0.94, 1.18)	0.98 (0.85, 1.14)	NA
Darunavir/ritonavir+tenofovir disoproxil fumarate/emtricitabine[b,d]	Darunavir 800 once daily	90 once daily	400 once daily	23	1.01 (0.96, 1.06)	1.04 (0.99, 1.08)	1.08 (0.98, 1.20)
	ritonavir 100 once daily				1.17 (1.01, 1.35)	1.25 (1.15, 1.36)	1.48 (1.34, 1.63)
	Emtricitabine 200 once daily				1.02 (0.96, 1.08)	1.04 (1.00, 1.08)	1.03 (0.97, 1.10)
	Tenofovir disoproxil fumarate 300 once daily				1.64 (1.54, 1.74)	1.50 (1.42, 1.59)	1.59 (1.49, 1.70)
Darunavir(boosted by ritonavir)	800/100 once daily	90 once daily	ND	23	1.02 (0.88, 1.19)	0.96 (0.84, 1.11)	0.97 (0.86, 1.10)
		ND	400 single dose	18	0.97 (0.94, 1.01)	0.97 (0.94, 1.00)	0.86 (0.78, 0.96)
Dolutegravir + tenofovir disoproxil fumarate/ emtricitabine[e]	dolutegravir 50 once daily	90 once daily	400 once daily	29	1.15 (1.07, 1.23)	1.13 (1.06, 1.20)	1.13 (1.06, 1.21)
	emtricitabine 200 once daily				1.02 (0.95, 1.08)	1.07 (1.04, 1.10)	1.05 (1.02, 1.09)
	Tenofovir disoproxil fumarate 300 once daily				1.61 (1.51, 1.72)	1.65 (1.59, 1.71)	2.15 (2.05, 2.26)

Co-administered Drug	Dose of Coadministered Drug (mg)	LDV Dose (mg)	SOF Dose (mg)	N	Mean Ratio (90% CI) of Coadministered drug PK With/Without Ledipasvir, Sofosbuvir or HARVONI No Effect=1.00		
					C_{max}	AUC	C_{min}
Tenofovir disoproxil fumarate/emtricitabine/efavirenz[e]	tenofovir disoproxil fumarate 300 once daily	90 once daily	400 once daily	15	1.79 (1.56, 2.04)	1.98 (1.77, 2.23)	2.63 (2.32, 2.97)
	emtricitabine 200 once daily				1.08 (0.97, 1.21)	1.05 (0.98, 1.11)	1.04 (0.98, 1.11)
	efavirenz 600 once daily				0.87 (0.79, 0.97)	0.90 (0.84, 0.96)	0.91 (0.83, 0.99)
Tenofovir alafenamide/elvitegravir/cobicistat/emtricitabine	tenofovir alafenamide 10 once daily	90 once daily	400 once daily	30	0.90 (0.73, 1.11)	0.86 (0.78, 0.95)	NA
	elvitegravir 150 once daily				0.98 (0.90, 1.07)	1.11 (1.02, 1.20)	1.46 (1.28, 1.66)
	cobicistat 150 once daily				1.23 (1.15, 1.32)	1.53 (1.45, 1.62)	3.25 (2.88, 3.67)
	emtricitabine 200 once daily				1.03 (0.96, 1.11)	0.97 (0.93, 1.00)	0.95 (0.91, 0.99)
Tenofovir disoproxil fumarate/emtricitabine/rilpivirine[f]	tenofovir disoproxil fumarate 300 once daily	90 once daily	400 once daily	14	1.32 (1.25, 1.39)	1.40 (1.31, 1.50)	1.91 (1.74, 2.10)
	emtricitabine once 200 daily				1.02 (0.98, 1.06)	1.05 (1.02, 1.08)	1.06 (0.97, 1.15)
	rilpivirine 25 once daily				0.97 (0.88, 1.07)	1.02 (0.94, 1.11)	1.12 (1.03, 1.21)
R-Methadone	30 to 130 daily	ND	400 once daily	14	0.99 (0.85, 1.16)	1.01 (0.85, 1.21)	0.94 (0.77, 1.14)
S-Methadone					0.95 (0.79, 1.13)	0.95 (0.77, 1.17)	0.95 (0.74, 1.22)
Norelgestromin	Norgestimate 0.180/0.215/0.2	90 once daily	ND	15	1.02 (0.89,	1.03 (0.90,	1.09 (0.91,

Co-administered Drug	Dose of Coadministered Drug (mg)	LDV Dose (mg)	SOF Dose (mg)	N	Mean Ratio (90% CI) of Coadministered drug PK With/Without Ledipasvir, Sofosbuvir or HARVONI No Effect=1.00		
					C_{max}	AUC	C_{min}
	5/ ethinyl estradiol 0.025 once daily				1.16)	1.18)	1.31)
		ND	400 once daily		1.07 (0.94, 1.22)	1.06 (0.92, 1.21)	1.07 (0.89, 1.28)
Norgestrel		90 once daily	ND		1.03(0.87, 1.23)	0.99 (0.82, 1.20)	1.00 (0.81, 1.23)
		ND	400 once daily		1.18 (0.99, 1.41)	1.19 (0.98, 1.45)	1.23 (1.00, 1.51)
Ethinyl estradiol		90 once daily	ND		1.40 (1.18, 1.66)	1.20 (1.04, 1.39)	0.98 (0.79, 1.22)
		ND	400 once daily		1.15 (0.97, 1.36)	1.09 (0.94, 1.26)	0.99 (0.80, 1.23)
Raltegravir	400 twice daily	90 once daily	ND	28	0.82 (0.66, 1.02)	0.85 (0.70, 1.02)	1.15 (0.90, 1.46)
		ND	400 single dose	19	0.57 (0.44, 0.75)	0.73 (0.59, 0.91)	0.95 (0.81, 1.12)
Simeprevir	150 once daily	30 once daily	ND	28	2.61 (2.39, 2.86)	2.69 (2.44, 2.96)	NA
Tacrolimus	5 single dose	ND	400 single dose	16	0.73 (0.59, 0.90)	1.09 (0.84, 1.40)	NA

NA = not available/not applicable, ND = not dosed.

a. All interaction studies conducted in healthy volunteers.

b. Data generated from simultaneous dosing with HARVONI. Staggered administration (12 hours apart) of atazanavir/ritonavir + tenofovir DF/emtricitabine or darunavir/ritonavir +tenofovir DF/ emtricitabine and HARVONI provided similar results.

c. Comparison based on exposures when administered as atazanavir/ritonavir + tenofovir DF/emtricitabine.

d. Comparison based on exposures when administered as darunavir/ritonavir + tenofovir DF/emtricitabine.

e. Administered as ATRIPLA.

f. Administered as EVIPLERA.

CLINICAL TRIALS

Overview of Clinical Studies

Genotype 1 CHC

The efficacy of HARVONI was evaluated in 2105 patients with genotype 1 CHC in four trials including one trial conducted in noncirrhotic treatment-naïve patients (ION-3), one trial in cirrhotic and noncirrhotic treatment-naïve patients (ION-1), and one trial in cirrhotic and noncirrhotic patients who failed prior therapy with an interferon-based regimen, including regimens containing an HCV protease inhibitor (ION-2) and one trial in patients with cirrhosis who failed prior therapy with a Peg-IFN+ribavirin regimen followed by a Peg-IFN+ribavirin+HCV protease inhibitor regimen (SIRIUS). Patients in these trials had compensated liver disease. All four trials evaluated efficacy of HARVONI with or without ribavirin.

Genotype 2, 3, 4, 5 or 6

The efficacy of HARVONI in patients with genotype 2, 3 ,4, 5 and 6 CHC was evaluated in the following clinical trials:

- Genotype 2 (LEPTON): treatment-naïve and treatment-experienced patients, with or without cirrhosis (N=26)
- Genotype 3 (ELECTRON-2): treatment-naïve and treatment-experienced patients with or without cirrhosis (N=101)
- Genotype 4:
  - Study 1119: treatment-naïve and treatment-experienced patients, with or without cirrhosis (N=44)
  - ION-4: HCV/HIV-1 coinfected patients, with or without cirrhosis (N=8)
- Genotype 5 (Study 1119): treatment- naïve and treatment-experienced patients, with or without cirrhosis (N=25)
- Genotype 6 (ELECTRON-2): treatment-naïve and treatment-experienced patients, with or without cirrhosis (N=25)

For patients with genotype 2, 4, 5, or 6 CHC, HARVONI was administered for 12 weeks without ribavirin. For patients-with genotype 3 CHC, HARVONI with or without ribavirin was administered for 12 weeks in treatment-naive patients and HARVONI with ribavirin was administered for 12 weeks in treatment-experienced patients.

HCV/HIV-1 Coinfection

The efficacy of HARVONI in HCV/HIV-1 coinfected patients was evaluated in an open-label Phase 3 trial (ION-4) that enrolled 335 patients with genotype 1 or 4 CHC, with or without cirrhosis, coinfected with HIV-1. All patients in the trial were treated with HARVONI for 12 weeks.

Patients Who Failed Prior Treatment with SOVALDI and Ribavirin, with or without Interferon

The efficacy of HARVONI in genotype 1 CHC patients who failed prior treatment with regimens containing SOVALDI was evaluated in two clinical trials. In Study 1118, patients who had

previously failed SOVALDI+RBV±Peg-IFN, with or without cirrhosis, were treated with HARVONI+RBV for 12 weeks (N=45). In Study ION-4, 13 patients who had failed SOVALDI+RBV were treated with HARVONI without ribavirin for 12 weeks.

Liver Transplant Recipients and/or Patients with Decompensated Cirrhosis

The efficacy of HARVONI in liver transplant recipients and/or patients with decompensated cirrhosis was evaluated in two open-label Phase 2 trials (SOLAR-1 and SOLAR-2) that enrolled 670 patients with genotype 1 and 4 CHC post-liver transplant and/or with decompensated cirrhosis. Patients in the two trials were treated with HARVONI+RBV for 12 or 24 weeks.

Serum HCV RNA values were measured during the clinical trials using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System in ION-3, ION-1, ION-2, SIRIUS and ION-4 studies or the COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) in ELECTRON-2, LEPTON, SOLAR-1, SOLAR-2, Study 1118 and 1119. The COBAS Taqman HCV test (version 2.0) for use with the High Pure System has a lower limit of quantification (LLOQ) of 25 IU permL and the COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) has a LLOQ of 15 IU per mL. Sustained virologic response (SVR) was the primary endpoint to determine the HCV cure rate which was defined as HCV RNA less than LLOQ at 12 weeks after the cessation of treatment.

Clinical Trials in Patients with Genotype 1 CHC

Treatment-Naïve Patients– ION-3 (Study 0108)

ION-3 was a randomised, open-label trial that evaluated 8 weeks of treatment with HARVONI with or without ribavirin and 12 weeks of treatment with HARVONI in treatment naïve non-cirrhotic patients with genotype 1 CHC. Patients were randomised in a 1:1:1 ratio to one of the three treatment groups and stratified by HCV genotype (1a vs 1b).

Demographics and baseline characteristics were balanced across the treatment groups. Of the 647 treated patients, the median age was 55 years (range: 20 to 75); 58% of the patients were male; 78% were White, 19% were Black; 6% were Hispanic or Latino; mean body mass index was 28 kg/m^2 (range: 18 to 56 kg/m^2); 81% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 80% had genotype 1a HCV infection; 73% had non-CC IL28B alleles (CT or TT).

Table 4presents the response rates for the treatment groups in the ION-3 trial.

Table 4 Response Rates in Study ION-3

	HARVONI 8 weeks (N=215)	**HARVONI+RBV8 weeks (N=216)**	**HARVONI 12 weeks (N=216)**
Overall SVR	94% (202/215)	93% (201/216)	96% (208/216)
Outcome for patients without SVR			
On-treatment virologic failure	0/215	0/216	0/216
Relapse[a]	5% (11/215)	4% (9/214)	1% (3/216)
Other[b]	≤1% (2/215)	3% (6/216)	2% (5/216)

a. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
b. Other includes patients who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

The 8-week treatment of HARVONI without ribavirin was noninferior to the 8-week treatment of HARVONI with ribavirin (treatment difference 0.9%; 95% confidence interval: -3.9% to 5.7%) and the 12-week treatment of HARVONI (treatment difference -2.3%; 97.5% confidence interval: -7.2% to 2.5%). Among patients with a baseline HCV RNA < 6 million IU/mL, the SVR was 97% (119/123) with 8-week treatment of HARVONI and 96% (126/131) with 12-week treatment of HARVONI.

Response rates for selected subgroups are presented in Table 5.

Table 5 SVR Rates for Selected Subgroups in ION-3

	HARVONI 8 Weeks (N = 215)	**HARVONI+RBV 8 Weeks (N = 216)**	**HARVONI 12 Weeks (N = 216)**
Genotype			
Genotype 1a	93% (159/171)	92% (159/172)	96% (165/172)
Genotype 1b	98% (42/43)	95% (42/44)	98% (43/44)
Viral Load (HCV RNA Log_{10} IU/ml)			
<800,000	97% (33/34)	96% (43/45)	96% (42/44)
≥800,000	93% (169/181)	92% (158/171)	95% (167/172)

Relapse rates by baseline viral load are presented in Table 6.

Table 6 Relapse rates by baseline viral load in study ION-3

	HARVONI 8 weeks (n = 215)	**HARVONI+RBV 8 weeks (n = 216)**	**HARVONI 12 weeks (n = 216)**
Number of responders at end of treatment	215	216	216
Baseline HCV RNAa			
HCV RNA < 6 million IU/mL	2% (2/123)	2% (3/137)	2% (2/131)
HCV RNA ≥ 6 million IU/mL	10% (9/92)	8% (6/77)	1% (1/85)

a. HCV RNA values were determined using the Roche TaqMan Assay; a patient's HCV RNA may vary from visit to visit.

Treatment-Naïve Adults with or without Compensated Cirrhosis ─ ION-1 (Study 0102)

ION-1 is an ongoing randomised, open-label trial to evaluate 12 and 24 weeks of treatment with HARVONI with or without ribavirin in 865 treatment naïve patients with genotype 1 CHC including those with cirrhosis. Patients were randomised in a 1:1:1:1 ratio to receive HARVONI for 12 weeks, HARVONI + ribavirin for 12 weeks, HARVONI for 24 weeks or HARVONI + ribavirin for 24 weeks. Randomisation was stratified by the presence or absence of cirrhosis and HCV genotype (1a vs 1b). The interim primary endpoint analysis for SVR only included all patients enrolled in the 12-week treatment groups (N = 431). SVR rates for all patients enrolled in the 24 week treatment groups (N= 434) were not available at the time of interim analysis.

Demographics and baseline characteristics were balanced across the treatment groups. Of the 865 treated patients, the median age was 54 years (range: 18 to 80); 59% of the patients were male; 85% were White, 12% were Black; 12% were Hispanic or Latino; mean body mass index was 27

kg/m^2 (range: 18 to 48 kg/m^2); 79% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 67% had genotype 1a HCV infection; 70% had non-CC IL28B alleles (CT or TT) and 16% had cirrhosis.

Table 7presents the response rates for the treatment groups of HARVONI with or without ribavirin for 12 weeks in the ION-1 trial.

Table 7 Response Rates in Study ION-1

	HARVONI 12 Weeks (N = 214)	**HARVONI + RBV 12 Weeks (N = 217)**
SVR[a]	99% (210/213)	97% (211/217)
Outcome for subjects without SVR		
On-Treatment Virologic Failure	0/213	0/217
Relapse[a]	<1% (1/212)	0/217
Other[b]	<1% (2/213)	3% (6/217)

a. Excluding one patient with genotype 4 infection
b. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
c. Other includes patients who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

Response groups for selected subgroups are presented in Table 8.

Table 8 SVR Rates for Selected Subgroups in Study ION-1

	HARVONI 12 Weeks (N = 214)	**HARVONI+RBV 12 Weeks (N = 217)**
Genotype		
Genotype 1a	98% (142/145)	97% (143/148)
Genotype 1b	100% (67/67)	99% (67/68)
Viral Load (HCV RNA Log_{10} IU/ml)		
<800,000	98% (44/45)	93% (41/44)
≥800,000	98 (165/169)	98% (170/173)
Cirrhosis[a]		
No	99% (176/177)	97% (177/183)
Yes	94% (32/34)	100% (33/33)

[a] Patients with missing cirrhosis status were excluded from this subgroup analysis.

Previously-Treated Adults with or without Compensated Cirrhosis – ION-2 (Study 0109)

ION-2 was a randomised, open-label trial that evaluated 12 and 24 weeks of treatment with HARVONI with or without ribavirin in genotype 1 HCV-infected patients with or without cirrhosis who failed prior therapy with an interferon-based regimen, including regimens containing an HCV protease inhibitor. Patients were randomised in a 1:1:1:1 ratio to receive HARVONI for 12 weeks, HARVONI + ribavirin for 12 weeks, HARVONI for 24 weeks or HARVONI + ribavirin for 24 weeks. Randomisation was stratified by the presence or absence of cirrhosis, HCV genotype (1a vs 1b) and response to prior HCV therapy (relapse/breakthrough vs nonresponse).

Demographics and baseline characteristics were balanced across the treatment groups. Of the 440 treated patients, the median age was 57 years (range: 24 to 75); 65% of the patients were male; 81% were White, 18% were Black; 9% were Hispanic or Latino; mean body mass index was 28 kg/m^2 (range: 19 to 50 kg/m^2); 89% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 79% had genotype 1a HCV infection; 88% had non-C/C IL28B alleles (CT or TT) and 20% had cirrhosis. Forty-seven percent (47%) of the patients failed a prior therapy of pegylated interferon and ribavirin. Among these patients, 49% were relapse/breakthrough and 51% were non-responder. Fifty-three percent (53%) of the patients failed a prior therapy of pegylated interferon and ribavirin with an HCV protease inhibitor. Among these patients, 62% were relapse/breakthrough and 38% were non-responder.

Table 9 presents the response rates for the treatment groups in the ION-2 trial.

Table 9 Response Rates in Study ION-2

	HARVONI 12 Weeks (N=109)	**HARVONI+RBV 12 Weeks (N=111)**	**HARVONI 24 Weeks (N=109)**	**HARVONI+RBV 24 Weeks (N=111)**
SVR	94% (102/109)	96% (107/111)	99% (108/109)	99% (110/111)
Outcome for subjects without SVR				
On-Treatment Virologic Failure	0/109	0/111	0/109	<1% (1/111)
Relapse	6% (7/108)	4% (4/111)	0/109	0/110
Other	0/109	0/111	<1% (1/109)	0/111

a. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

b. Other includes patients who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

Response rates for selected subgroups are presented in Table 10.

Table 10 SVR Rates for Selected Subgroups in Study ION-2

	HARVONI 12 Weeks (N=109)	**HARVONI+RBV 12 Weeks (N=111)**	**HARVONI 24 Weeks (N=109)**	**HARVONI+RBV 24 Weeks (N=111)**
Genotype				
Genotype 1a	95% (82/86)	95% (84/88)	99% (84/85)	99% (87/88)
Genotype 1b	87% (20/23)	100% (23/23)	100% (24/24)	100% (23/23)
Viral Load (HCV RNA Log_{10} IU/ml)				
<800,000	83% (5/6)	100% (13/13)	100% (16/16)	100% (15/15)
≥800,000	94% (97/103)	96% (94/98)	99% (92/93)	99% (95/96)
Cirrhosis[a]				
No	95% (83/87)	100% (88/88)	99% (85/86)	99% (88/89)
Yes	86% (19/22)	82% (18/22)	100% (22/22)	100% (22/22)
Prior HCV Therapy				
Peg-IFN + RBV	93% (40/43)	96% (45/47)	100% (58/58)	98% (58/59)

	HARVONI 12 Weeks (N=109)	HARVONI+RBV 12 Weeks (N=111)	HARVONI 24 Weeks (N=109)	HARVONI+RBV 24 Weeks (N=111)
HCV protease inhibitor + Peg-IFN + RBV	94% (62/66)	97% (62/64)	98% (49/50)	100% (51/51)
Response to prior HCV Therapy				
Relapse/Breakthrough	95% (57/60)	97% (63/65)	100% (60/60)	98% (59/60)
Nonresponder	92% (45/49)	96% (44/46)	98% (48/49)	100% (51/51)

a. Patients with missing cirrhosis status were excluded from this subgroup analysis.

Relapse rates for selected subgroups are presented in Table 11.

Table 11 Relapse rates for selected subgroups in study ION-2

	HARVONI 12 weeks (n = 109)	HARVONI+RBV 12 weeks (n = 111)	HARVONI 24 weeks (n = 109)	HARVONI+RBV 24 weeks (n = 111)
Number of responders at end of treatment	**108**	**111**	**109**	**110**
Cirrhosis				
No	5% (4/86)	0% (0/88)[b]	0% (0/86)[b]	0% (0/88)
Yes	14% (3/22)	18% (4/22)	0% (0/22)	0% (0/22)
Presence of baseline NS5A resistance-associated substitutions[c]				
No	3% (3/91)	2% (2/94)	0% (0/96)	0% (0/95)
Yes	24% (4/17)	12% (2/17)	0% (0/13)	0% (0/14)

a. These 4 non-cirrhotic relapsers all have baseline NS5A resistance-associated polymorphisms

b. Patients with missing cirrhosis status were excluded from this subgroup analysis.

c. NS5a resistance-associated polymorphisms include any change at NS5A positions 24, 28, 30, 31, 58, 92 or 93

Previously-Treated Adults with Compensated Cirrhosis – SIRIUS (Study 0121)

SIRIUS was a randomised, double-blind and placebo-controlled trial that evaluated the efficacy of HARVONI + ribavirin for 12 weeks or HARVONI without ribavirin for 24 weeks in genotype 1 HCV-infected patients with compensated cirrhosis who failed prior therapy with a Peg-IFN + RBV regimen followed by a subsequent Peg-IFN +RBV + an HCV protease inhibitor regimen. Patients were randomised in a 1:1 ratio to receive placebo for 12 weeks followed by HARVONI + ribavirin for 12 weeks or HARVONI for 24 weeks. Randomisation was stratified by HCV genotype (1a vs 1b) and response to prior HCV therapy (never achieved HCV RNA less than LLOQ vs achieved HCV RNA less than LLOQ).

Demographics and baseline characteristics were balanced across the treatment groups. Of the 155 randomised patients, the median age was 56 years (range: 23 to 77); 74% of the patients were male; 97% were White; mean body mass index was 27 kg/m^2 (range: 19 to 47 kg/m^2); 63% had genotype 1a HCV infection; 94% had non-C/C IL28B alleles (CT or TT). All patients (with the exception of 1) met the protocol defined definition of cirrhosis as defined by biopsy, transient

elastography (>12.5 kPa) or FibroTest score >0.75 and an AST:platelet ratio index (APRI) >2. One patient discontinued therapy while on placebo, and was not included in the efficacy analysis.

The SVR rate was 96% (74/77) and 97% (75/77) in patients treated with HARVONI + ribavirin for 12 weeks and HARVONI for 24 weeks without ribavirin, respectively. All 5 patients who did not achieve SVR12 relapsed.

Clinical Trials in Patients with Genotype 2, 3 ,4, 5, or 6 CHC

HARVONI has been evaluated for the treatment of non-genotype 1 infection in a number of Phase 2 and 3 studies, as summarised below.

The clinical studies enrolled patients with or without cirrhosis, who were treatment-naïve or with prior treatment failure after therapy with PEG-IFN + ribavirin +/- an HCV protease inhibitor.

For genotype 2, 4, 5 and 6 infection, therapy consisted of HARVONI without ribavirin, given for 12 weeks (Table 12). For genotype 3 infection, HARVONI was given with or without ribavirin, also for 12 weeks (Table 13).

Table 12 Response rates (SVR12) with HARVONI for 12 weeks in patients with genotype 2, 4, 5 and 6 HCV infection

Study	Genotype	N	Treatment Experienced % (n/N)	SVR12		Relapse[a]
				Overall	Cirrhosis	
Study 1468 (LEPTON)	2	26	19% (5/26)	96% (25/26)[b]	100% (2/2)	0% (0/25)
Study 1119	4	44	50% (22/44)	93% (41/44)	100% (10/10)	7% (3/44)
Study 0115 (ION-4)	4	8	50% (4/8)	100% (8/8)	0% (0/0)	0% (0/0)
Study 1119	5	41	49% (20/41)	93% (38/41)[c]	89% (8/9)	5% (2/40)
Study 0122 (ELECTRON-2)	6	25	0% (0/25)	96% (24/25)	100% (2/2)	4% (1/25)[d]

a. The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.
b. The patient who did not achieve SVR12 withdrew consent and discontinued from the study after receiving a single dose of HARVONI.
c. One patient was lost to follow up.
d. Patient discontinued study treatment early at approximately Week 8 of 12.

Table 13 Response rates (SVR12) in patients with genotype 3 infection (Study 0122 ELECTRON-2)

	HARVONI+RBV 12 weeks		HARVONI 12 weeks	
	SVR12	Relapse[a]	SVR12	Relapse[a]
Treatment-naïve	100% (26/26)	0% (0/26)	64% (16/25)	33% (8/24)
Patients without cirrhosis	100% (20/20)	0% (0/21)	71% (15/21)	25% (5/20)
Patients with cirrhosis	100% (6/6)	0% (0/5)	25% (1/4)	75% (3/4)
Treatment-experienced	82% (41/50)[b]	16% (8/49)	NS	NS
Patients without cirrhosis	89% (25/28)	7% (2/27)	NS	NS
Patients with cirrhosis	73% (16/22)	27% (6/22)	NS	NS

NS: Not studied

a. The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.
b. One patient experienced on-treatment virologic failure.

Clinical Trials in Patients with HCV/HIV-1 Coinfection

ION-4 was an open-label clinical trial that evaluated the safety and efficacy of 12 weeks of treatment with HARVONI without ribavirin in HCV treatment-naïve and treatment-experienced patients with genotype 1 or 4 CHC who were coinfected with HIV-1. Treatment-experienced patients had failed prior treatment with Peg-IFN + RBV, Peg-IFN + RBV + an HCV protease inhibitor or SOVALDI + RBV ± Peg-IFN. Patients were on a stable HIV-1 antiretroviral therapy that included emtricitabine + tenofovir DF, administered with efavirenz, rilpivirine or raltegravir.

Of the 335 treated patients, the median age was 52 years (range: 26 to 72); 82% of the patients were male; 61% were White; 34% were Black; mean body mass index was 27 kg/m^2 (range: 18 to 66 kg/m^2); 75% had genotype 1a HCV infection; 2% had genotype 4 infection; 76% had non-C/C IL28B alleles (CT or TT); and 20% had compensated cirrhosis. Fifty-five percent (55%) of the patients were treatment-experienced.

Table 14 presents the response rates in the ION-4 trial after 12 weeks of HARVONI treatment.

Table 14 Study ION-4: Response Rates after 12 Weeks of Treatment in Patients with Genotype 1 or 4 CHC with or without Cirrhosis Who Are Coinfected with HIV-1

	HARVONI 12 Weeks (N=335)
SVR	96% (321/335)[a]
Outcome for Patients without SVR	
On-Treatment Virologic Failure	<1% (2/335)
Relapse[b]	3% (10/333)
Other[c]	<1% (2/335)

a. 8 subjects with genotype 4 HCV infection were enrolled
b The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
c. Other includes patients who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

SVR rates were 94% (63/67) in patients with cirrhosis and 98% (46/47) in patients who were previously-treated and had cirrhosis.

No patient had HIV-1 rebound during the study and no clinically meaningful changes in CD4+ cell count from baseline were observed.

Clinical Trials in SOVALDI+RBV±Peg-IFN Treatment Failures

The efficacy of HARVONI in patients who had previously failed treatment with SOVALDI+RBV±Peg-IFN is supported by two clinical trials. In Study 1118, 44 patients with genotype 1 infection who had previously failed a SOVALDI+Peg-IFN+RBV or a SOVALDI+RBV regimen were treated with HARVONI + RBV for 12 weeks; the SVR was 100% (44/44). In Study ION-4, 13 HCV/HIV-1 coinfected patients with genotype 1 HCV infection who had failed a SOVALDI+RBV regimen were enrolled; the SVR was 100% (13/13) after 12 weeks of treatment with HARVONI without ribavirin.

There are no data in non-genotype 1 patients who have previously failed a sofosbuvir-containing regimen.

Clinical Trials in Liver Transplant Recipients and/or Patients with Decompensated Cirrhosis

SOLAR-1 and SOLAR-2 were two open-label clinical trials that evaluated 12 and 24 weeks of treatment with HARVONI in combination with ribavirin in genotype 1 and 4 HCV-infected patients who have undergone liver transplantation and/or who have decompensated liver disease. The two trials were identical in study design. Patients were enrolled in one of the seven groups based on liver transplantation status and severity of hepatic impairment (see Table 13). Patients with a CPT score >12 were excluded. Within each group, patients were randomised in a 1:1 ratio to receive HARVONI + RBV for 12 weeks or HARVONI + RBV for 24 weeks.

Demographics and baseline characteristics were balanced across the treatment groups. Of the 670 treated patients, the median age was 59 years (range: 21 to 81); 77% of the patients were male; 91% were White; mean body mass index was 28 kg/m^2 (range: 18 to 49 kg/m^2); 94% and 6% had genotype 1 and 4 HCV infection, respectively; 78% of the patients failed a prior HCV therapy.97 Among the patients who had decompensated cirrhosis (pre- or post-transplant), 64% and 36% were CPT class B and C at screening, respectively,98 and 24% had a baseline Model for End Stage Liver Disease (MELD) score greater than 15.97.

Table 15 presents the pooled response rates of SOLAR-1 and SOLAR-2 in patients with genotype 1 CHC.

Table 15 Pooled Response Rates in Study SOLAR-1 and SOLAR-2 in Patients with Genotype 1 CHC

	HARVONI+RBV 12 Weeks (N = 307)[a,b]	**HARVONI+RBV 24 Weeks (N = 307)[a,b]**
Pre-transplant		
CPT B	87% (45/52)	92% (46/50)
CPT C	88% (35/40)	83% (38/46)
Post-transplant		
Metavir score F0-F3	95% (94/99)	99% (99/100)
CPT A	98% (55/56)	96% (51/53)
CPT B	89% (41/46)	96% (43/45)
CPT C	57% (4/7)	78% (7/9)
Fibrosis cholestatic hepatitis	100% (7/7)	100% (4/4)

a. Twelve patients transplanted prior to post-treatment Week 12 with HCV RNA<LLOQ at last measurement prior to transplant were excluded.
b. Two patients who did not have decompensated cirrhosis and had also not received a liver transplant were excluded due to failure to meet the inclusion criteria for any of the treatment groups.

Among the 26 patients with genotype 1 CHC who did not achieve SVR12 after 12 weeks of treatment, 14 patients relapsed and the other 12 subjects were considered treatment failure due to death (N=11) or withdrawal of consent (N=1). Among the 19 patients with genotype 1 CHC who did not achieve SVR12 after 24 weeks of treatment, 6 patients relapsed and the other 13 patients were considered treatment failure due to death (N=11), withdrawal of consent (N=1) or early discontinuation after 8 days on treatment (N=1).

Among 40 patients with genotype 4 CHC enrolled in SOLAR-1 and SOLAR-2 studies, SVR12 were 92% (11/12) and 100% (10/10) in post-transplant patients without decompensated cirrhosis treated for 12 or 24 weeks, respectively. No subjects relapsed. SVR12 were 60% (6/10) and 75% (6/8) in patients with decompensated cirrhosis (pre- and post-liver transplantation) treated for 12 or 24 weeks, respectively. Of the 7 patients who failed to achieve SVR12, 3 relapsed, all of whom had decompensated cirrhosis and were treated with HARVONI+ribavirin for 12 weeks.

Changes in MELD and CPT score from baseline to post-treatment Week 12 were analysed for all patients with decompensated cirrhosis (pre- or post-transplant) who achieved SVR12 and for whom data were available (N=123) to assess the effect of SVR12 on hepatic function:

Change in MELD score: Among those who achieved SVR12 with 12 weeks treatment with HARVONI+RBV, 57% (70/123) and 19% (23/123) had an improvement or no change in MELD score from baseline to post-treatment week 12, respectively; of the 32 patients whose MELD score was ≥ 15 at baseline, 59% (19/32) had a MELD score < 15 at post-treatment Week 12. Improvement in MELD score was driven largely by improvement in bilirubin.

Change in CPT: Among those who achieved SVR12 with 12 weeks treatment with HARVONI+RBV, 60% (74/123) and 34% (42/123) had an improvement or no change of CPT scores from baseline to post-treatment week 12, respectively; of the 32 subjects who had CPT C cirrhosis at baseline, 53% (17/32) had CPT B cirrhosis at post-treatment Week 12; of the 88 patients who had CPT B cirrhosis at baseline, 25% (22/88) had CPT A cirrhosis at post-treatment Week 12. Improvement in CPT score was driven largely by improvement in albumin and bilirubin.

INDICATIONS

HARVONI (ledipasvir/sofosbuvir fixed-dose combination) is indicated for the treatment of chronic hepatitis C (CHC) infection in adults.

(see PRECAUTIONS and CLINICAL TRIALS sections for information on the available data for HCV patients of each genotype, see DOSAGE AND ADMINISTRATION section for recommended regimens and treatment durations for different patient subgroups).

CONTRAINDICATIONS

HARVONI tablets are contraindicated in patients with known hypersensitivity to the active substance or to any other component of the tablets.

HARVONI is a fixed-dose combination of ledipasvir and sofosbuvir. HARVONI should not be administered concurrently with other medicinal products containing any of the same active components.

PRECAUTIONS

Symptomatic Bradycardia When Coadministered with Amiodarone

Postmarketing cases of symptomatic bradycardia, as well as fatal cardiac arrest and cases requiring pacemaker intervention, have been reported when amiodarone is coadministered with HARVONI. Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown.

Coadministration of amiodarone with HARVONI is not recommended. For patients taking amiodarone who have no other alternative, viable treatment options and who will be coadministered HARVONI:

- Counsel patients about the risk of symptomatic bradycardia
- Cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Patients who are taking HARVONI who need to start amiodarone therapy due to no other alternative, viable treatment options should undergo similar cardiac monitoring as outlined above.

Due to amiodarone's long half-life, patients discontinuing amiodarone just prior to starting HARVONI should also undergo similar cardiac monitoring as outlined above.

Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion or memory problems.

Use with Potent P-gp Inducers

Drugs that are potent P-gp inducers (e.g., rifampicin, St. John's Wort) may significantly decrease ledipasvir and sofosbuvir plasma concentration leading to reduced therapeutic effect of HARVONI. Rifampicin and St. John's Wort should not be used with HARVONI.

HCV/HBV (hepatitis B virus) Coinfected Patients

The safety and efficacy of HARVONI has not been established in patients coinfected with HBV.

Genotype-specific activity (genotype 2 and 3)

The clinical data to support the use of HARVONI in patients infected with HCV genotype 2 are limited.

The clinical data to support the use of HARVONI in patients infected with HCV genotype 3 are limited. The relative efficacy of a 12 week regimen consisting of ledipasvir/sofosbuvir + ribavirin, compared to a 24 week regimen of sofosbuvir + ribavirin has not been investigated.

Treatment of patients with prior exposure to HCV direct-acting antivirals

In patients who fail treatment with HARVONI, selection of NS5A resistance mutations that substantially reduce the susceptibility to ledipasvir is seen in the majority of cases. Limited data indicate that such NS5A mutations do not revert on long-term follow-up. There are presently no data to support the effectiveness of retreatment of patients who have failed HARVONI with a subsequent regimen that contains an NS5A inhibitor. Similarly, there are presently no data to support the effectiveness of NS3/4A protease inhibitors in patients who previously failed prior therapy that included an NS3/4A protease inhibitor. Such patients may therefore be dependent on other drug classes for clearance of HCV infection.

Use with Certain HIV Antiretroviral Regimens

HARVONI has been shown to increase tenofovir exposure. The potential risks and benefits associated with coadministration of tenofovir DF with HARVONI should be considered, particularly in patients at increased risk for renal dysfunction (See Drug Interactions Section).

Impairment of Fertility

Ledipasvir: Ledipasvir had no adverse effects on mating and fertility in rats. In female rats, the mean number of corpora lutea and implantation sites were slightly reduced at maternal exposures 6-fold the exposure in humans at the recommended clinical dose. At the no observed effect level, AUC exposure to ledipasvir was approximately 7- and 3-fold, in males and females, respectively, the human exposure at the recommended clinical dose.

Sofosbuvir: Sofosbuvir had no effects on embryo-foetal viability or on fertility when evaluated in rats. At the highest dose tested, AUC exposure to the predominant circulating metabolite GS-331007 was approximately 5-fold the exposure in humans at the recommended clinical dose.

Use in Pregnancy: HARVONI (Pregnancy Category B1)

There are no adequate and well-controlled studies with HARVONI in pregnant women. Because animal reproduction studies are not always predictive of human response, HARVONI should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Pregnancy: Use with ribavirin (Pregnancy Category X)

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. When HARVONI is used in combination with ribavirin extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Women of childbearing potential and their male partners must use effective contraception during treatment and for approximately six months after the treatment has concluded as recommended in the product information for ribavirin. If ribavirin is co-administered with HARVONI, the contraindications regarding use of ribavirin apply (refer to ribavirin product information).

Ledipasvir: No effects on fetal development have been observed in rats and rabbits at the highest doses tested. In the rat and rabbit, AUC exposure to ledipasvir was 5- and 2-fold, respectively, the exposure in humans at the recommended clinical dose.

In a rat pre- and postnatal study, at a maternally toxic dose, the developing rat offspring exhibited mean decreased body weight and body weight gain when exposed *in utero* (via maternal dosing) and during lactation (via maternal milk) at a maternal exposure approximately 4 times the

exposure in humans at the recommended clinical dose. There were no effects on survival, physical and behavioural development and reproductive performance in the offspring at maternal exposures similar to the exposure in humans at the recommended clinical dose.

Sofosbuvir: No effect on fetal development has been observed in rats and rabbits at the highest doses tested. In the rat and rabbit, exposure to the predominant circulating metabolite GS-331007 was approximately 10-fold and 28-fold the exposure in humans at the recommended clinical dose, respectively.

Use in Lactation

When administered to lactating rats, ledipasvir was detected in the plasma of suckling rats likely due to excretion of ledipasvir via milk. Ledipasvir had no effects on the nursing pups. The predominant circulating metabolite of sofosbuvir (GS-331007) was the primary component observed in the milk of lactating rats, without effect on nursing pups. It is not known whether ledipasvir, sofosbuvir or metabolites of sofosbuvir are present in human breast milk. Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue treatment with HARVONI, taking into account the importance of the therapy to the mother.

Use in Children

Safety and effectiveness of HARVONI in children less than 18 years of age have not been established.

Use in the Elderly

Clinical trials of HARVONI included 351 patients aged 65 and over. The response rates observed for subjects over 65 years of age were similar to that of younger patients across treatment groups. No dose adjustment of HARVONI is warranted in elderly patients. In general, caution should be exercised when administering HARVONI in elderly patients, reflecting the greater frequency of anaemia, decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Genotoxicity

Ledipasvir was not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and *in vivo* rat micronucleus assays.

Sofosbuvir was not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and in vivo mouse micronucleus assays.

Carcinogenicity

A carcinogenicity study in make and female mice does not indicate any carcinogenicity potential of ledipasvir administered at doeses up to 300 mg/kg/day. Exposure to ledipasvir in this study was up to 26 x higher than the clinical exposure at 90 mg ledipasvir. A carcinogenicity study in rats is ongoing.

Carcinogenicity studies in mice and rats do not indicate any carcinogenicity potential of sofosbuvir administered at doses up to 200 mg/kg/day in male mice and 600 mg/kg/day in female mice, and 750 mg/kg/day in rats. Exposure to GS-331007 in these studies in mice was up to 7 x (male) and 30 x (female), and in rats up to 13 x (male) and 17 x (female) higher than the clinical exposure at 400 mg sofosbuvir.

INTERACTIONS WITH OTHER MEDICINES

As HARVONI contains ledipasvir and sofosbuvir, any interactions that have been identified with these agents individually may occur with HARVONI.

After oral administration of HARVONI, sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic extraction. Hydrolytic prodrug cleavage and sequential phosphorylation steps results in formation of the pharmacologically active uridine nucleoside analog triphosphate. Dephosphorylation of nucleotide metabolites results in conversion to the predominant circulating metabolite GS-331007 that accounts for approximately 85% of total systemic exposure. In clinical pharmacology studies, both sofosbuvir and GS-331007 were monitored for purposes of pharmacokinetic analyses.

Potential for HARVONI to Affect Other Drugs

Ledipasvir is an inhibitor of drug transporter P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters. Ledipasvir is an inhibitor of transporters OATP1B1, OATP1B3 and BSEP only at concentrations exceeding those achieved in clinic. Ledipasvir is not an inhibitor of transporters MRP2, MRP4, OCT2, OAT1, OAT3, MATE1, and OCT1. The drug-drug interaction potential of ledipasvir is primarily limited to the process of intestinal absorption. Clinically relevant transporter inhibition by ledipasvir in the systemic circulation is not expected due to its high protein binding. Sofosbuvir and GS-331007 are not inhibitors of drug transporters P-gp, BCRP, MRP2, BSEP, OATP1B1, OATP1B3 and OCT1 and GS-331007 is not an inhibitor of OAT1, OCT2, and MATE1.

Ledipasvir, sofosbuvir and GS-331007 are not inhibitors or inducers of CYP or UGT1A1 enzymes.

Potential for Other Drugs to Affect HARVONI

Ledipasvir and sofosbuvir are substrates of drug transporters P-gp and BCRP while GS-331007 is not. Drugs that are potent P-gp inducers (e.g. rifampicin or St. John's Wort) may decrease ledipasvir and sofosbuvir plasma concentrations leading to reduced therapeutic effect of HARVONI and thus should not be used with HARVONI (see Warnings and Precautions for Use: Use with Potent P-gp Inducers). Coadministration with drugs that inhibit P-gp and/or BCRP may increase ledipasvir and sofosbuvir plasma concentrations without increasing GS-331007 plasma concentration; HARVONI may be coadministered with P-gp and/or BCRP inhibitors. Neither ledipasvir nor sofosbuvir is a substrate for hepatic uptake transporters OCT1, OATP1B1 or OATP1B3. GS-331007 is not a substrate for renal transporters including organic anion transporter OAT1 or OAT3, or organic cation transporter OCT2.

Ledipasvir is subject to slow oxidative metabolism via an unknown mechanism. *In vitro*, no detectable metabolism of ledipasvir by CYP enzymes has been observed. Biliary excretion of unchanged ledispavir is a major route of elimination. Sofosbuvir is not a substrate for CYP and

UGT1A1 enzymes. Clinically significant drug interactions with HARVONI mediated by CYP or UGT1A1 enzymes are not expected.

Established and Other Potentially Significant Drug Interactions

Table 16 provides a listing of established or potentially clinically significant drug interations. The drug interactions described are based on studies conducted with either HARVONI, the components of HARVONI (ledipasvir and sofosbuvir) as individual agents, or are predicted drug interations that may occur with HARVONI. This table is not all inclusive.

Table 16 Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Acid Reducing Agents:	¯ ledipasvir ↔ sofosbuvir ↔ GS-331007	Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of ledipasvir.
Antacids (e.g. aluminum and magnesium hydroxide)		It is recommended to separate antacid and HARVONI administration by 4 hours.
H_2-receptor antagonists[c]		H2-receptor antagonists may be administered simultaneously with or staggered from HARVONI at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors[c]		Proton-pump inhibitor doses comparable to omeprazole 20 mg can be administered simultaneously with HARVONI or up to 2 hours after taking HARVONI. Proton-pump inhibitors should not be taken before HARVONI.
Antiarrhythmics: amiodarone	Effect on amiodarone, ledipasvir, and sofosbuvir concentrations unknown	Coadministration of amiodarone with HARVONI may result in symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with HARVONI is not recommended; if coadministration is required, cardiac monitoring is recommended (see Precautions: Symptomatic Bradycardia when Coadministered with Amiodarone)
digoxin	↑ digoxin	Coadministration of HARVONI with digoxin may increase the concentration of digoxin. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when coadministered with HARVONI.
Anticonvulsants carbamazepine phenytoin phenobarbital oxcarbazepine	¯ ledipasvir ¯ sofosbuvir	Coadministration of HARVONI with carbamazepine, phenytoin, phenobarbital, or oxcarbazepine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended.
Anticoagulants: dabigatran etexilate	Interaction not studied. Expected:	Clinical monitoring, looking for signs of bleeding and anaemia, is recommended when dabigatran etexilate is co-administered with HARVONI. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
	↑ dabigatran ↔ledipasvir ↔ sofosbuvir ↔ GS-331007	
Antimycobacterials: rifabutin rifampicin[c] rifapentine	¯ ledipasvir ¯ sofosbuvir ¯ GS-331007	Coadministration of HARVONI with rifabutin or rifapentine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended. HARVONI should not be used with rifampicin, a potent intestinal P-gp inducer.
Antiretrovirals: tenofovir disoproxil fumarate	- tenofovir	HARVONI has been shown to increase tenofovir exposure. The potential risks and benefits associated with coadministration of tenofovir DF with HARVONI should be considered, particularly in patients at increased risk for renal dysfunction. Patients receiving tenofovir DF and HARVONI concomitantly should be monitored for adverse reactions associated with tenofovir DF. Refer to the tenofovir DF-containing product's prescribing information for recommendations on renal monitoring.
tipranavir/ritonavir	¯ ledipasvir	Coadministration of HARVONI with tipranavir/ritonavir is expected to decrease the concentration of ledipasvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended.
HCV Products: simeprevir[c]	- ledipasvir - simeprevir	Concentrations of ledipasvir and simeprevir are increased when simeprevir is coadministered with ledipasvir. Coadministration of HARVONI with simeprevir is not recommended
Herbal Supplements: St. John's Wort *(Hypericum perforatum*)	¯ ledipasvir ¯ sofosbuvir	HARVONI should not be used with St. John's Wort, a potent intestinal P-gp inducer (see Precautions for Use: Use with Potent P-gp Inducers)
HMG-CoA Reductase Inhibitors: rosuvastatin	- rosuvastatin	Coadministration of HARVONI with rosuvastatin may significantly increase the concentration of rosuvastatin which is associated with increased risk of myopathy, including rhabdomyolysis. Coadministration of HARVONI with rosuvastatin is not recommended.
Other statins	Expected - Statins	Interactions cannot be excluded with other HMG-CoA reductase inhibitors. When co-administered with HARVONI, a reduced dose of statins should be considered and careful monitoring for statin adverse reactions should be undertaken.

a. This table is not all inclusive.

b. ↑ = increase, ↓ = decrease

c. These interactions have been studied in healthy adults.

Drugs without Clinically Significant Interactions with HARVONI

Based on drug interaction studies conducted with the components of HARVONI (ledipasvir or sofosbuvir) or HARVONI, no clinically significant drug interactions have been either observed or are expected when HARVONI is combined with the following individual drugs: abacavir, atazanavir/ritonavir, cyclosporin, darunavir/ritonavir, dolutegravir, efavirenz, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, lamivudine, methadone, oral contraceptives, pravastatin, raltegravir, rilpivirine, tacrolimus or verapamil.

Effects on ability to drive and use machines

No studies on the effects of HARVONI on the ability to drive and use machines have been performed.

ADVERSE EFFECTS

Clinical Trials

The safety assessment of HARVONI in patients with genotype 1 CHC is based on pooled data from three Phase 3 clinical trials (ION-3, ION-1 and ION-2) including 215, 539 and 326 patients who received HARVONI for 8, 12 and 24 weeks, respectively; and 216, 328 and 328 patients who received HARVONI + ribavirin combination therapy for 8, 12 and 24 weeks, respectively.

The proportion of patients who permanently discontinued treatment due to adverse events was 0%, <1% and 1% for patients receiving HARVONI for 8, 12 and 24 weeks, respectively; and <1%, 0%, and 2% for patients receiving HARVONI + ribavirin combination therapy for 8, 12 and 24 weeks, respectively.

No adverse drug reactions specific to HARVONI have been identified. In clinical trials ION-1, ION-2, and ION-3, fatigue, headache and nausea were the most common (incidence ≥ 10%) treatment emergent adverse events reported in patients treated with 8 or 12 weeks of HARVONI which are the recommended regimens for patients (see DOSAGE and ADMINISTRATION). The type of treatment emergent adverse events observed during 24 weeks of treatment with HARVONI was consistent with those observed during 8 or 12 weeks of treatment but the frequency of adverse events is generally higher in the 24 week treatment group than the 8 or 12 week treatment groups. When HARVONI was studied with ribavirin, the most frequent adverse events to HARVONI + ribavirin combination therapy were consistent with the known safety profile of ribavirin, without increasing the frequency or severity of the expected adverse events.

Table 17 lists adverse reactions (adverse events assessed as causally related by the investigator, all grades) observed in ≥5% of patients receiving 8, 12, or 24 weeks treatment with HARVONI in clinical trials. The majority of adverse reactions presented in Table 15 occurred at severity of grade 1.

Table 17 Adverse Reactions (All Grades) Reported in ≥5% of Patients Receiving 8, 12 or 24 Weeks of Treatment with HARVONI

	HARVONI 8 weeks (n = 215)	**HARVONI 12 weeks (n = 539)**	**HARVONI 24 weeks (n = 326)**
Fatigue	16%	13%	18%

	HARVONI 8 weeks (n = 215)	HARVONI 12 weeks (n = 539)	HARVONI 24 weeks (n = 326)
Headache	11%	14%	17%
Nausea	6%	7%	9%
Diarrhoea	4%	3%	7%
Insomnia	3%	5%	6%

The safety of HARVONI with or without ribavirin in treatment-experienced genotype 1 patients with compensated cirrhosis was compared to placebo in Study SIRIUS. Patients were randomised to receive 24 weeks of HARVONI without ribavirin or 12 weeks of placebo followed by 12 weeks of HARVONI+ribavirin. Table 18 presents the adverse reactions, as defined above, that were reported more frequently (≥5%) in patients during the first 12 weeks of treatment in the HARVONI 24 week treatment group or in patients treated with 12 weeks of HARVONI + ribavirin, compared with those reported for 12 weeks of placebo. The majority of the adverse reactions presented in Table 18 were Grade 1 or 2 in severity.

Table 18 Adverse Reactions Reported ≥5% More Frequent in Treatment-Experienced Patients with Cirrhosis Receiving HARVONI for the First 12 Weeks in the HARVONI 24 Week Treatment Arm or HARVONI+RBV for 12 Weeks Than Placebo for 12 weeks

	HARVONI (first 12 weeks of 24 week treatment) (N=78)	HARVONI+RBV 12 weeks (N=76)	Placebo 12 weeks (N=77)
Fatigue[a]	41%	38%	25%
Headache	27%	13%	16%
Cough	4%	11%	1%
Irritability	8%	7%	1%
Dyspnea	1%	9%	1%

a. Includes preferred terms fatigue and asthenia.

No adverse drug reactions specific to HARVONI were identified from the clinical trials conducted in patients with genotype 2, 3, 4, 5 or 6 CHC.

HCV/HIV-1 Coinfection

No adverse drug reactions specific to HARVONI were identified from an open-label trial (ION-4) in which patients with HCV/HIV-1 coinfection received treatment with HARVONI for 12 weeks (N=335).

Liver Transplant Recipients and/or Patients with Decompensated Cirrhosis

No adverse drug reactions specific to HARVONI were identified from two open-label trials (SOLAR-1 and SOLAR-2) in which liver transplant recipients and/or patients with

decompensated cirrhosis received HARVONI with ribavirin for 12 or 24 weeks (N=670). The adverse events observed were consistent with expected clinical sequelae of liver transplantation and/or decompensated liver disease, or the known toxicity profile of ribavirin.

Decreases in haemoglobin to less than 10 mg/dL and 8.5 mg/dL during treatment were experienced by 39% and 13% of patients treated with HARVONI+ribavirin, respectively. Ribavirin was discontinued in 15% of the subjects. Due to improved organ function, 7% of liver transplant recipients had a dose modification of their immunosuppressive agents.

Post Martketing Surveillance

In addition to adverse reactions from clinical studies, the following possible adverse reactions were also identified during postapproval use of HARVONI. Because these reactions were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Cardiac Disorders

Symptomatic bradycardia (when amiodarone is coadministered with HARVONI) (see **Precautions: Symptomatic Bradycardia when Coadministered with Amiodarone**)

Skin and Subcutaneous Tissue Disorders

Rash

DOSAGE AND ADMINISTRATION

The recommended dose of HARVONI tablets is one tablet, taken orally, once daily with or without food.

The recommended treatment regimen and duration for HARVONI is provided in Table 19.

For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in Table 19.

Table 19 Recommended Treatment Regimen and Duration for HARVONI (including the co-adminsitration of ribavirin for certain subgroups)

HCV Genotype	Patient Population	Treatment Regimen and Duration
Genotype 1	Treatment-naïve without cirrhosis	HARVONI 8 or 12 weeks[a]
	Treatment-naïve with cirrhosis	HARVONI 12 weeks
	Treatment-experienced[b] without cirrhosis	HARVONI 12 weeks
	Treatment-experienced[b] with cirrhosis	HARVONI + RBV 12 or 24 weeks[c]
	Treatment-naïve and treatment experienced[b] liver transplant recipients with compensated liver disease	HARVONI + RBV 12 weeks
	Treatment-naïve and treatment-experienced[b] with decompensated cirrhosis, irrespective of transplantation status	HARVONI + RBV 12 weeks
Genotype 4, 5, 6	Treatment-naïve without cirrhosis	HARVONI 12 weeks
	Treatment-naïve with cirrhosis	HARVONI 12 weeks
	Treatment-experienced[b] without cirrhosis	HARVONI 12 weeks
	Treatment-experienced[b] with cirrhosis	HARVONI + RBV 12 or 24 weeks[c]
	Treatment-naïve and treatment experienced[b] liver transplant recipients with compensated liver disease	HARVONI + RBV 12 weeks

a HARVONI for 8 weeks can be considered in treatment-naïve genotype 1 patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL

b Treatment-experienced[b] patients who have failed a peginterferon alfa + ribavirin based regimen with or without an HCV protease inhibitor or a regimen that included SOVALDI + ribavirin with or without peginterferon alfa

c 24 weeks should be considered for patients who are ineligible for, intolerant of, or unwilling to take ribavirin and for treatment-experienced patients with compensated cirrhosis who are at high risk of clinical disease progression.

There are insufficient data to determine the optimal treatment duration for genotype 4 patients with decompensated liver disease.

Concomitant Ribavirin Dose

When HARVONI is used in combination with ribavirin, the daily dose of ribavirin is 1,000 mg for patients weighing <75 kg and 1,200 mg for those weighing ≥75 kg, except for patients with decompensated cirrhosis who should receive 600 mg. Ribavirin is administered orally in two divided doses with food. Refer to ribavirin prescribing information for ribavirin dose modifications.

Children and Adolescents up to 18 Years of Age: No data are available on which to make a dose recommendation for children < 18 years of age.

Elderly: No dose adjustment is warranted for elderly patients

Renal impairment: No dose adjustment of HARVONI is required for patients with mild or moderate renal impairment. No dose recommendations can be given for patients with severe renal impairment eGFR<30mL/min/1.73m^2 or with end stage renal disease requiring haemodialysis due to higher exposure of the predominant sofosbuvir metabolite (see PHARMACOKINETCS).

Hepatic impairment: No dose adjustment of HARVONI is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C) (see PHARMACOKINETICS). Safety and efficacy of HARVONI have not been established in patients with decompensated cirrhosis.

OVERDOSAGE

The highest documented doses of ledipasvir and sofosbuvir were 120 mg twice daily for 10 days and a single dose of 1200 mg, respectively. In these healthy volunteer studies, there were no untoward effects observed at these dose levels, and adverse events were similar in frequency and severity to those reported in the placebo groups. The effects of higher doses/exposures are not known.

No specific antidote is available for overdose with HARVONI. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with HARVONI consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. Haemodialysis is unlikely to result in significant removal of ledipasvir since ledipasvir is highly bound to plasma protein. Haemodialysis can efficiently remove the predominant circulating metabolite of sofosbuvir, GS-331007, with an extraction ratio of 53%.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) and 0800 764 766 (New Zealand).

PRESENTATION AND STORAGE CONDITIONS

HARVONI is available as a fixed-dose combination tablet. Each tablet contains 90 mg ledipasvir and 400 mg sofosbuvir and are orange diamond shaped, film coated with "GSI" on one side and "7985" on the other side.

HARVONI is supplied in high density polyethylene (HDPE) bottles containing 28 tablets and is closed with a child resistant closure.

HARVONI should be stored below 30 °C.

NAME AND ADDRESS OF THE SPONSOR

Gilead Sciences Pty Ltd
Level 6, 417 St Kilda Road
Melbourne, Victoria 3004

POISON SCHEDULE OF THE DRUG

S4

DATE OF INCLUSION ON ARTG:

13 May 2015

DATE OF MOST RECENT AMENDMENT:

14 November 2016